UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/745,883	12/21/2000	Hans-Ulrich Demuth	20784-5	1277

21710 7590 01/23/2003

BROWN, RUDNICK, BERLACK & ISRAELS, LLP.
BOX IP, 18TH FLOOR
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/745,883	DEMUTH ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-15 are pending.

Applicants' amendment filed October 21, 2002 (Paper No. 17) is acknowledged. Applicants' response has been fully considered. Claims 1, 2, 9, 11, 13 and 14 have been amended, and a new claim 15 has been added. Thus, claims 1-15 are examined.

Oath/Declaration

2. In response to the defective oath/declaration, applicants indicate a new oath/declaration will be submitted in compliance with 37 CFR 1.67 (a). The oath or declaration is defective because it lists the foreign application DE 19828114.5 under 35 U.S.C. § 120 and/or 121, it should claim foreign priority benefits under 35 U.S.C. § 119(a)-(d). Regarding the continuation application PCT/EP99/04381, it can be listed under 35 U.S.C. § 120 and/or 365 (c).

Information Disclosure Statement

3. The references listed in the information Disclosure Statement (IDS) filed June 17, 2002 have been search by the examiner, however, they have not been found to date. Only the references listed in the previous IDS were considered. Please resubmit the references which were not signed by the Examiner.

Objection Withdrawn

4. The previous objection to the specification is withdrawn in view of the newly substituted specification which has been entered.

5. The previous objection to claims 1 and 4 is withdrawn in view of the amendment to the claim, and applicants' response at page 25 in Paper No. 17.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

6. The previous rejection of claims 1-3, 5, 6 and 8-13, under 35 U.S.C.112, second paragraph, regarding the term "C is an unstable inhibitor of DP IV", "consisting of.....or...", lacking essential steps in claims 9 and 10, or non-elected diseases in claim 13, is withdrawn in view of applicants' amendment to the claims, and applicants' response at pages 26-28 in Paper No. 17.

Claim Rejections - 35 USC § 102

7. The previous rejection of claims 2, 3 and 5, under 35 U.S.C.102 (b) as being anticipated by Bachovchin *et al.* (WO 93/08259) is withdrawn in view of applicants' amendment to the claims, and applicants' response at page 28 in Paper No. 17.

8. The previous rejection of claims 2, 3, 5 and 7, under 35 U.S.C.102 (b) as being anticipated by Bachovchin *et al.* (WO 95/11689) is withdrawn in view of applicants' amendment to the claims, and applicants' response at pages 29 in Paper No. 17.

Claim Objections

9. Claims 9 and 11 are objected to because of the use of "A is an amino acid B is a chemical...". A comma "," should be inserted after the phrase "A is an amino acid".

10. Claims 9 and 14 are objected to because there is no period "." at the end of the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 11-13 are rejected under 35 U.S.C. 112, first paragraph, because while a method of treating an autoimmune disease, where DP IV plays a role, by administering a compound comprising an unstable dipeptide inhibitor of DP IV is enabled for T-cell mediated pathogenic activity related arthritis, rejection of transplanted organs, SLE and AIDS (blocking HIV entry into CD-26 bearing cells) as indicated in the prior art, does not reasonably provide enablement for a method for treating all disorders, all metabolic disorders, or diseases associated with diabetes mellitus as cited in claim 13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 11-13 encompass a method of treating disorders in mammals (claim 11), the scope of the claim would have included genetic disorders, the treatment of which is not described so as to enable the scope of the claim; a method of treating metabolic disorders of humans (claim 12), the scope would have included such disorders as Garrod's inborn errors of metabolism, the treatment of which is not enabled by the current application which does not discuss these disorders, See for example, Stryer (1975) Biochemistry (W.H. Freeman and Company, San Franciso) which discloses a metabolic disorder Alcaptonuria for which the current application does not enable for treatment; or treating disorders associated with diabetes mellitus in mammals (claim 13) by modulating the DP IV enzymatic activity, comprising administering the compound A-B-C, where C is an unstable inhibitor of DP IV containing a dipeptide having a C-terminus active carbonyl group. The specification, however, only discloses cursory conclusions (page 3, lines 15-17; page 5, lines 7-14) without data supporting the findings, which state that the compounds of unstable inhibitors of DP IV can be used for the treatment of disorders in

mammals by modulating the DP IV enzymatic activity, especially metabolic disorders associated with diabetes mellitus. There are no indicia that the present application enables the full scope in view of treating a disorder in mammals as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the treating conditions for various disorders, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

There are no working examples indicating the claimed methods in association with various disorders in mammals.

(3). The state of the prior art and relative skill of those in the art:

The prior art (WO 93/08259; WO 95/11689) indicates administration of a compound comprising an unstable dipeptide inhibitor of DP IV can treat an autoimmune disease such as T-cell mediated pathogenic activity related arthritis, rejection of transplanted organs, SLE and AIDS (blocking HIV entry into CD-26 bearing cells), where DP IV plays a role, however, the

general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the treatment of various disorders in mammals to be considered enabling for variants, but it does not.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of treating disorders in mammals, metabolic disorders of humans, or disorders associated with diabetes mellitus in mammals by modulating the DP IV enzymatic activity, comprising administering the compound A-B-C, where C is an unstable inhibitor of DP IV containing a dipeptide having a C-terminus active carbonyl group. The specification also indicates the compounds containing the unstable inhibitors of DP IV can be used for treating various disorders, especially metabolic disorders associated with diabetes mellitus, and the masked inhibitor is more effective than the non-masked inhibitors because the masked compound produces a marked improvement in glucose tolerance in Wistar rats (page 3, lines 15-21). However, the specification has not demonstrated the use of any compound containing unstable DP IV inhibitor in treating any disorder, any metabolic disorder, or any metabolic disorder associated with diabetes mellitus, nor has indicated the treating conditions such as the dose and the effect of the compound. There is no disclosure indicating the end point of the treatment using the compound containing an unstable inhibitor of DP IV. Moreover, there are no working examples indicating the use and the effect of the compound in treating various disorders. Since the specification fails to provide sufficient guidance on treating conditions of various disorders, one skilled in the art would not know how to treat the diseases, thus, it is

necessary to have additional guidance/teachings and to carry out further experimentation to assess the effects of the compounds.

(5). Predictability or unpredictability of the art:

The claim encompasses using a compound comprising an unstable inhibitor of DP IV to treat various disorders in mammals, since the treating conditions for various disorders are not sufficiently described, the outcome of the claimed invention is highly unpredictable.

(6). Nature of the Invention

The scope of the claim includes treating all disorders (claim 11), metabolic disorders (claim 12), and disorders associated with diabetes mellitus (claim 13) using a compound comprising an unstable inhibitor of DP IV, however the specification has not demonstrated the treatment of these disorders. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example is lacking, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the compound comprising an unstable inhibitor of DP IV in treating various disorders, various metabolic disorders or disorders associated with diabetes mellitus.

In response, applicants indicate "the written description" only requires describing the invention to one of ordinary skill in the art, it does not require demonstrating the use of a compound, and the applicants must merely provide sufficient details to allow one skilled in the art to practice the invention. The comments in the response have been assessed in view of the current enablement rejection, and the comments are unpersuasive. Applicants further assert that the specification has disclosed the method of administration, dosing and the effect of the

compound (pages 5, 8-9 of the specification; pages 25-26 of the response). The argument is not found persuasive because the specification only indicates the amount of the inhibitor for inhibiting DP IV in vivo is different in individual cases, and the compound in the pharmaceutical composition can be used for treatment of disorders by modulating the DP IV activity, the specification does not provide sufficient guidance and teachings on treating conditions such as effective dose for treating metabolic disorders, nor indicates the effect of the inhibitor in the treatment, as indicated in the section above, without such guidance and teachings, one skilled in the art would not know how to practice the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 1-15 are indefinite because of the use of the term "a dipeptide derivative", "dipeptidyl alkyl ketone derivative" or "a fluoro alkyl ketone derivative". The term "dipeptide derivative", "dipeptidyl alkyl ketone derivative" or "a fluoro alkyl ketone derivative" renders the claim indefinite, it is unclear what the compound is as to "a derivative", and how different the derivative is from the parent compound. Claims 2-8, 10 and 12-15 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend. Claim 1 describes one type of compound having the general formula A-B-C, thus, use of "A compound" instead of "compounds" is suggested.

In response, applicants indicate the specification has clearly define a dipeptide derivative as having an active carbonyl group at the C-terminus, which is represented by dipeptidyl chloroalkyl ketone, dipeptidyl boronic acid, dipeptidyl cyanide compound or dipeptidyl pyridinium methyl ketone compound (page 8, lines 19-25 of the specification; page 27 of the response). The argument is not persuasive because the specification indicates a dipeptide derivative comprises an active carbonyl group at the C-terminus, thus, the term would also include other derivations. Use of "a dipeptide compound" is suggested.

14. Claim 4 is indefinite because of the use of the terms "Thia" and "Pyr", it is not clear what the term means. A full chemical name should be indicated.

15. Claims 11-13 are indefinite because they lack essential steps as claimed in the method of treating disorders. The omitted steps are: the effective amount of the compound used, and the outcome for the treatment. Claims 12 and 13 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend. Claims 11 and 12 are also indefinite as to "disorders" or 'metabolic disorders", it is not clear what disorder is intended.

In response, applicants indicate the specification has disclosed each organism will release the exact amount of inhibitor that is necessary to inhibit the amount of DP IV that is present, which is different in individual cases (pages 27-28 of the response). The argument is not found persuasive because the claim does not recite the essential steps such as effective dose used and the outcome for the treatment, thus it is not clear how to practice the claimed method.

16. Claim 14 recites the limitation "dipeptide cyanide" in line 4. There is insufficient antecedent basis for this limitation in the claim because dipeptide cyanide does not contain an active carbonyl group.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1, 8-12 and 15 are rejected under 35 U.S.C. 102(b) as anticipated by Bachovchin *et al.* (WO 93/08259).

Bachovchin *et al.* disclose an inhibitory compound of DP IV having a structure of Group I-Group II, where Group I contains unblocked peptide, and Group II contains a boronate, a phosphonate or a trifluoroalkyl ketone group which is covalently to Pro or a Pro analog (pages 3-5), and the preferred inhibitory compound includes an amino acid sequence having the cleavage site of a DP IV substrate, thus the cleavage product of the inhibitory compound also inhibits DP IV (page 8; claim 1). The inhibitory compound is admixed with a pharmaceutical acceptable carrier (page 5, lines 25-26; claims 8 and 9). The compound can be administered orally and used for treating an autoimmune disease such as T-cell mediated pathogenic activity related arthritis, rejection of transplanted organs, SLE and AIDS, or delaying catabolism of growth releasing factor, where DP IV regulates the progress of the disease (page 21, lines 7-30; claims 10, 11, 12 and 15).

18. Claims 1, 8-12 and 15 are rejected under 35 U.S.C. 102(b) as anticipated by Bachovchin *et al.* (WO 95/11689).

Bachovchin *et al.* disclose an inhibitory compound of DP IV having a structure of Group I-Group II, where Group I contains unblocked peptide, and Group II contains a boronate, a phosphonate or a fluoroalkyl ketone group which is covalently to Pro or a Pro analog (page 2, line 33-page 5, line 22; Fig. 1), and the preferred inhibitory compound includes an amino acid sequence having the cleavage site of a DP IV substrate, thus the cleavage product of the inhibitory compound also inhibits DP IV (page 8, line29- page 9, line 17; claim 1). The inhibitory compound is admixed with a pharmaceutical acceptable carrier (page 5, lines 20-21; claims 8 and 9). The compound can be administered orally and used for blocking entry of HIV into CD26-bearing cells, where DP IV regulates the progress of the disease (page 7, lines 7-20; claims 10, 11, 12 and 15).

In response, applicants indicate Bachovchin *et al.* (WO 93/08259 and WO 95/11689) disclose the dipeptides having boroPro moiety as the unstable DP IV inhibitors, and the claims have been amended to the dipeptide having C-terminal active carbonyl group. The argument is not found persuasive because Bachovchin *et al.* also teach the compounds containing dipeptides with a fluoroalkyl ketone group, thus the claims are still anticipated by the reference.

19. Claim 8 recites "the compounds comprise a pharmaceutical composition for oral administration, wherein said composition comprises customary pharamaceutical carriers or excipients", which is not the usual way describing a pharmaceutical composition. Perhaps claim 8 can be stated as follows:

A pharmaceutical composition for oral administration comprising the compound of claim 1 and a customary pharmaceutical carrier or excipient.

Conclusion

20. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

Christopher S. F. Low
CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

***
January 17, 2003